Zinc and the Gastroenterologist

Implications for the Practitioner

Noel W. Solomons

Zinc is an important trace element, essential to human nutrition and of concern to the physicians or practitioners involved in the care of patients with digestive diseases. The intestinal absorption of zinc involves specialized transport mechanisms; an inborn error of metabolism, acrodermatitis enteropathica, results in a primary zinc malabsorption. Dietary factors such as plant phytins and fiber also interfere with the bioavailability of zinc. Although a simple and unequivocal laboratory test for assessing clinical zinc status is not available, it is known that a number of hepatic, pancreatic, and gastrointestinal diseases can alter zinc metabolism and can lead to impaired zinc nutriture. With increased application of total parenteral alimentation, it has been noted that the nutrient solutions are often deficient in zinc; cases of overt iatrogenic zinc depletion have been observed frequently. Recently, the AMA has formulated recommendations for intravenous zinc replacement during parenteral nutrition. Zinc supplementation is also indicated when primary or secondary clinical zinc deficiency is detected. However, as all administration of therapeutic zinc may cause gastric irritation and copper depletion, caution must be exercised in its use. Increased awareness of trace mineral metabolism and nutritional requirements will improve the care of patients with digestive diseases.

The importance of zinc in nutrition and its therapeutic potential has only recently been realized. Zinc has become important not only in scientific investigation but also in the health-food industry and among food faddists.

Noel W. Solomons, M.D.: Assistant Professor of Clinical Nutrition, Massachusetts Institute of Technology, Cambridge; Affiliated Scientist, Division of Human Nutrition and Biology, Institute of Nutrition of Central America and Panama; and Research Associate, Gastroenterology Section, University of Chicago (Pritzker) School of Medicine.

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The total body content of zinc in the adult is 2–3 g, making it the second most abundant trace mineral after iron. Insufficient attention has been given to the potential importance of zinc to patients with diseases of the gastrointestinal tract. This article reviews the practical implications of zinc for the practitioner.

Zinc has a primary nutritional and biochemical role as a component of metalloenzymes. Some more familiar zinc enzymes include carbonic anhydrase, alkaline phosphatase, and carboxypeptidase A. Several enzymes of cell replication and protein synthesis are also zinc-dependent. Clinical zinc deficiency syndromes have been recognized in man. In some cases they are secondary to other diseases or are iatrogenic conditions. In other cases

they may be due primarily to dietary factors such as inadequate zinc intake—for example, in total parenteral nutrition—or reduced biological availability of dietary zinc as occurs with a high-fiber diet.

In chronic zinc depletion occurring before puberty, growth retardation, hypogonadism, and skin lesions are characteristic and respond to zinc therapy. In acute zinc deficiency, skin lesions, alopecia, mental disturbances, and impaired host defenses are prominent. Abnormalities of taste and smell have been reported in both acute an chronic zinc deficiency, as has impaired healing of surgical wounds. Of specific interest to the gastroenterologist is the morphological change in the intestinal mucosal cell and functional abnormalities. Diarrhea is a feature of severe clinical zinc deficiency in cattle and in man. Recently, impaired absorption of folic acid, particularly of conjugated polyglutamate folates, was observed in human volunteers fed an experimental zinc-deficient diet.

ZINC ABSORPTION AND EXCRETION

Absorption

The exact site of zinc absorption in the intestine is unknown. Experiments in animals have identified each of the portions of the small bowel, duodenum, jejunum, and ileum, as the site of preferential zinc absorption. It is generally thought that an intestinal binding ligand of low molecular weight, perhaps of pancreatic origin, plays an important role in the mucosal uptake of zinc. Many suggestions have been put forth about the nature of this zinc-binding ligand, including prostaglandin E_2, citrate, and picanilic acid. Although it has not yet been identified, it is accepted that zinc absorption involves a zinc-binding ligand.

The exact site of zinc absorption in the intestine is unknown

There is also mounting evidence that zinc absorption, like that of iron, is homeostatically controlled by the nutritional state of the individual with respect to the mineral. In experimental animals the absorption of radiozinc is inversely proportional to the circulating zinc concentration. The mechanism of control is not precisely understood, but metallothionein, a low-molecular-weight soluble protein, may play a role. Metallothioneins are rapidly-turning-over proteins with a high affinity for binding zinc (and copper, cadmium, and mercury); metallothioneins can be induced in the mucosa by either parenteral or oral administration of zinc. It has been suggested that when zinc nutriture is adequate in an individual, metallothionein traps zinc in the enterocyte, preventing its entry into the circulation and ensuring its eventual excretion with the desquamation of the mucosal cell. This hypothesis is not confirmed. Zinc is transported from the serosa to the liver in a protein-bound form, either with albumin or transferrin. It has been estimated that the liver clears two-thirds of the newly absorbed portal zinc with each passage.

Biological Availability of Zinc

Many dietary constitutents influence the bioavailability of zinc. Dietary fiber binds zinc in the intestine, rendering it unavailable for absorption. Calcium and plant phytins also impair the absorption of zinc. Copper and iron, which are chemically similar divalent cations, appear to share common absorptive pathways and therefore compete with zinc in the intestine for absorption. Iron seems to be more biologically significant, as we have found in our laboratories that dietary ratios of non-heme iron to zinc of 3:1 substantially reduce zinc absorption. The unleavened whole-wheat breads that are consumed as the staple food in rural Iran and Egypt are exceedingly rich in fiber and phytates and are well known to inhibit zinc availability to the point that a proportion of the children develop dwarfism and hypogonadism because of zinc deficiency. Evidence from Guatemala suggest that the traditional diet of southern Mexico and Central America, based on corn tortillas and beans, has a potent inhibitory effect on zinc absorption. Even some foods common to the mixed diet of the United States, such as milk, cheese, coffee, celery, lemon, and hamburgers on a bun, have been noted to impair the absorption of extrinsically added zinc (1,2).

Red meats have a zinc content of about 60 μg/g (which is the same as that of whole grain), but the zinc from meat is much more bioavailable to the individual because of the absence of inhibitory factors. Atlantic oysters are the richest known source of zinc, with a content approaching 1.5 mg/g of tissue. We have used fresh-frozen oysters in human absorption experiments, and find that the absorption of zinc is similar to that of inorganic zinc salts. On the other hand, human milk and bovine milk are relatively deficient in zinc, but the zinc in human breast milk has been shown to be superior to that in cow's milk. Two factors might be involved: first, cow's milk is four times richer in calcium, an inhibitor of zinc absorption; second, in human milk the zinc appears to be largely associated with a low-molecular-weight ligand identical to the one found in the intestine.

Excretion

The feces are the primary route of zinc output, and zinc excretion in intestinal and pancreatic secretions is primarily responsible for the maintenance of zinc balance. Various gastrointestinal diseases can markedly increase zinc losses. Urine is generally a minor excretory pathway for zinc, but in certain conditions, such as following burns, surgery, or trauma, or in various hepatic diseases, the increased urinary zinc output can affect total body balance.

ZINC METABOLISM IN LIVER DISEASE

Alcoholic Cirrhosis

Low circulating levels of zinc, decreased hepatic concentrations of zinc, and pathologically increased urinary excretion of zinc are well-documented alterations in zinc metabolism in alcholoic cirrhosis. Isotopic turnover studies, the most precise and reliable index of zinc nutriture, have confirmed zinc depletion. In addition, there is evidence that the albumin of cirrhotic patients has a lessened affinity for zinc. Night blindness is a common finding in cirrhotic patients.

...aberrations of taste and smell in cirrhotics may be caused by zinc deficiency

Recently, workers at the University of Maryland found that vitamin A therapy *per se* will not correct the dark adaptation abnormalities in cirrhotic patients, but zinc supplementation, with or without retinol therapy, will correct the defect in 2–4 weeks. They concluded that zinc deficiency in cirrhotics leads to reduced activity of retinol dehydrogenase, a zinc-dependent enzyme in the retina involved in the interconversion of visual pigments in the rods and cones (3). The aberrations of taste and smell in cirrhotic individuals may also be caused by zinc deficiency. Finally, studies from the Veterans Hospital in Nebraska suggest that the intestinal absorption of oral zinc in patients with alcholic cirrhosis is impaired. (4).

Viral Hepatitis

Viral hepatitis is accompanied by increased urinary excretion of zinc. Some studies have also reported transiently decreased plasma zinc. The characteristic loss of taste acuity in hepatitis may also be zinc related, as it corresponds to the period of maximum zinc depression. Retinol-binding protein and vitamin A levels are also acutely and transiently depressed during the icteric phase of hepatitis. Since retinol-binding protein is purportedly very sensitive to the zinc status of experimental animals, zinc deficiency may play a role in the hypovitaminemia A of viral hepatitis.

Wilson's Disease

Wilson's disease (hepatolenticular degeneration) is, of course, a disease of abnormal copper accumulation. The effective treatment for Wilson's disease is chelation therapy with D(-)penicillamine to increase mobilization of copper from stores and excretion of copper in the urine. Normal hepatic copper concentrations have been restored after 7 or more years of chelation therapy. Penicillamine is not specific for copper, however, and other divalent minerals such as zinc are also removed from the body. In one reported case, severe clinical zinc deficiency in a patient receiving penicillamine was resolved with oral zinc therapy (5).

ZINC METABOLISM IN PANCREATIC DISEASE

The digestive enzyme, carboxypeptidase A, is a zinc metalloenzyme. The exocrine pancreas is an organ of voluminous protein synthesis and turnover, and requires adequate zinc nutrition. It has been suggested that the zinc-binding ligand originates from pancreatic secretions. In experimental animals, zinc depletion leads to pancreatic lipase dysfunction and steatorrhea. In a case report from Denmark, a zinc-responsive increase in lipase secretion was observed in a patient with pancreatic insufficiency and zinc deficiency (6). Investigations of zinc nutrition in cystic fibrosis of the pancreas have shown in incidence of zinc deficiency in most, but not all; the studies. Moreover, it is thought that the growth retardation of children with cystic fabrosis may be related to impaired zinc nutrition, but no studies have shown a reversal with zinc supplementation.

ZINC METABOLISM IN GASTROINTESTINAL DISEASE

Esophageal Carcinoma

Studies in Hong Kong have shown a high prevalence of zinc deficiency among patients with esophageal carcinoma (7). In laboratory animals, zinc deficiency potentiated the carcinogenic effect of a chemical nitrosamine in the experimental induction of esophageal malignancies. The presence of nitrosamines in the U.S. diet, presumably from bacon and other cured meats with nitrite preservatives, was studied recently at Massachusetts Institute of Technology. The combination of zinc deficiency and nitrosamine consumption may be involved in the induction of esophageal cancer in the U.S.

Gastric Ulcer

A number of drug regimens have recently been reported to be effective in the treatment of benign gastric ulcers. The practioner should be aware, however, of some interesting studies from Australia reporting a significantly faster reduction in ulcer crater size in patients receiving zinc sulfate (220 mg tid) as compared to placebo in a double-blind controlled trial (8). In instances in which other drugs of proven efficacy in gastric ulcer healing are contraindicated, or in the ulcer patient who is idiosyncratically resistant to standard therapy, zinc sulfate treatment offers an alternative.

Malabsorption

Small-intestinal disease can also influence zinc nutrition and metabolism. Malabsorption syndrome, for instance, produces zinc malabsorption and is associated with depressed circulating levels of zinc. Depressed plasma zinc has been reported in patients with celiac disease, both

untreated and under the control of gluten restriction. The rise in plasma zinc after an oral dose of zinc sulfate in patients with jejunoileal bypass procedures was markedly depressed, showing impaired absorption in short-bowel syndromes. Moreover, inflammatory bowel diseases (specifically, regional enteritis and granulomatous colitis) have been associated with low plasma and hair zinc concentrations and abnormalities of taste acuity in hospitalized patients. Growth-retarded preadolescent patients with Crohn's disease show remarkably low circulating zinc levels; it has been suggested that zinc might be one of the nutrients that limits the growth velocity of some children with inflammatory bowel disease. Although zinc malabsorption is considered to be the cause of low zinc levels in the malabsorption syndrome and inflammatory bowel disease, one should not discount a possible contribution of excessive zinc loss from the associated protein-losing enteropathy or of mediated internal redistribution of zinc from circulation to liver.

Table 1. *Gastrointestinal Diseases Reported to be Associated With Altered Zinc Metabolism*

Hepatic
Alcoholic cirrhosis
Viral hepatitis
Wilson's disease treated with penicillamine
Pancreatic
Alcoholic pancreatic insufficiency
Cystic fibrosis
Gastrointestinal
Esophageal carcinoma
Malabsorption syndromes
Jejunoileal by-pass
Celiac disease
Inflammatory bowel disease (Crohn's)
Acrodermatitis enteropathica

Acrodermatitis Enteropathica

In the past five years, evidence of a specific genetic zinc malabsorption syndrome has emerged. Acrodermatitis enteropathica is a non-sex-linked inborn error of metabolism that appears early in life and presents as "failure to thrive," with diarrhea, alopecia, increased susceptibility to infection, mental apathy, and characteristic acrofacial skin lesions. Malabsorption is also a frequent component.

Investigations by British dermatologists led to the discovery that zinc supplementation would relieve all of these manifestations (9). The findings have been amply confirmed around the world. Specific zinc absorption tests with radiozinc have documented impaired absorption of zinc. The exact mechanism is unknown, but the reduction or alteration of the intraluminal zinc-binding ligands has received the most emperical support. The classical observation that breast milk ameliorated the symptoms of acrodermatitis enteropathica can now be explained; the zinc in human milk is already associated with a low-molecular-weight zinc-binding ligand as discussed above, and hence the zinc is available for absorption even by individuals with this disease. An experimental animal model for acrodermatitis enteropathica in Fresian cattle with an analogous zinc-responsive zinc malabsorption will help us to understand this important, albeit rare, gastrointestinal and dermatological disease.

Table 1 lists the digestive diseases associated with low circulating plasma zinc levels.

TOTAL PARENTERAL ALIMENTATION

Total parenteral alimentation (TPA) is being used increasingly as a way of maintaining nutritional intake in a number of surgical, oncological, and gastrointestinal conditions. Zinc is *not* included in commercial water-soluble vitamin–mineral mixtures for parenteral administration. The zinc content of commercial amino acid or protein hydrolysate preparations is highly variable, with concentrations varying as much as 0.1–4 mg/liter of solution. Thus, most TPA regimens do not provide an adequate intake of zinc. Moreover, the severe catabolic conditions that often require the administration of intravenous alimentation can also increase zinc losses. Similarly, the anabolism induced in the nutritionally depleted patient can put a stress on marginal zinc reserves.

As a consequence of these factors, cases of acute zinc deficiency in which circulating zinc levels of less than 10 μg/dl have been observed in patients undergoing TPA. Moreover, a progressive decline in plasma zinc concentration was detected in studies of individuals on TPA at the University of Chicago (10) and the Mayo Clinic (11). In the specific situation of TPA administration, therefore, *changes* in circulating zinc concentrations are a relatively reliable index of changes in zinc nutriture due to deficient intakes, and serial monitoring of circulating zinc concentration is indispensible in managing the patient on TPA.

ASSESSMENT OF ZINC NUTRITURE

A persistent problem for the physician is the difficulty in making a clinical assessment of zinc nutriture. Table 2 lists the indices that have been proposed for the evaluation of zinc status in man. An exhaustive discussion of these indices has been published elsewhere (12).

Despite earlier claims to the contrary, it has now become eminently clear that plasma or serum zinc concentraion is not an unequivocal index of the zinc nutriture of the individual! Insofar as circulating zinc is gener-

A persistent problem... is the difficulty in making a clinical assessment of zinc nutriture

ally low in true zinc depletion, it is a useful measure. But zinc levels may also become depressed because of reduced levels of serum-binding proteins or reduced binding affinity for zinc, or because of mediated redistribution of zinc from the circulation to the liver during acute inflammatory or infectious stress. Care must be taken in obtaining the plasma or serum sample because hemolysis can release zinc from red cells into the plasma or serum, artifactually elevating the concentration. A further source of error is contamination from syringes, tubes, pipettes, etc, during processing and handling of the sample.

Many of the other indices listed are either experimental in nature or are beyond the scope of most clinical laboratories. Urinary zinc output is reported to fall in the presence of zinc deficiency, and urinary zinc is very easy to assay. The potential for exogenous contamination of the sample is great, however, and when hyperzincuria is the *cause* of the zinc deficiency, zinc excretion in the urine is elevated even in the face of a total-body depletion. Salivary zinc is a relatively new parameter. It has a diurnal pattern so that samples must be taken at a certain time of day, but it represents a definite, as yet partially explored, potential as an index of zinc nutriture.

Hair zinc concentration is another useful index. It is subject to environmental contamination, and is dependent upon a relatively normal rate of hair growth. The processing and analysis is laborious and subject to contamination, but as an index of zinc nutriture it is generally preferable to a random plasma or serum zinc determination. Newer, nondestructuve analytic techniques which leave the hair intact during analysis promise more rapid, precise, and meaningful measurements of hair zinc. It is hoped, as experience is gained with the new and experimental procedures, and as the importance of zinc nutriture is recognized, that hospitals and diagnostic centers will make available the more elaborate and specific tests of zinc nutriture.

Table 2. *Assessment of Zinc Nutriture in Man*

Elemental Analyses
- Plasma or serum (circulating) zinc
- Erythrocyte zinc
- Leukocyte zinc
- Hair zinc (whole digest method)
- Hair zinc (nondestructive methods)
- Salivary zinc
- Skin zinc
- Fingernail zinc
- Sweat zinc
- 24-hour urinary zinc output

Whole-Body Zinc Estimates
- Zinc retention (balance or isotopic)
- Zinc turnover (isotopic)

Functional/Biochemical Indices
- Serum alkaline phosphatase
- Red cell carbonic anhydrase
- Salivary "gustin"
- Serum retinol-binding protein
- Serum ribonuclease

Functional/Physiological Indices
- Red cell uptake of ^{65}Zn in vitro
- Neutrophil or macrophage chemotaxis
- Taste acuity
- Quantitative dark adaptation (Zinc-Vit A axis)
- Quantitative wound healing
- Linear growth during periods of expected rapid growth (infancy, adolescence)

THERAPEUTIC CONSIDERATIONS

Oral Zinc Administration

There are times when the physician is called upon to prescribe therapeutic zinc for his patients. Zinc is indicated for acrodermatitis enteropathica, zinc depletion due to chelation therapy in Wilson's disease, and when there is biochemical evidence of zinc deficiency in conditions predisposing to a secondary impairment of zinc nutriture. The most commonly dispensed preparation is 220-mg capsules of zinc sulfate containing 50 mg of elemental zinc. Zinc acetate and gluconate have been recommended, but no conclusive evidence for their superiority over zinc sulfate has been presented. When taken on an empty stomach, zinc salts can produce gastrointestinal side effects including dyspepsia, nausea, and epigastric burning. In addition, gastric erosion and hemorrhage after zinc sulfate ingestion has recently been reported (15). In the past, zinc capsules were taken with meals. We now know that this results in reduced bioavailability of the mineral. Alternatively, 110 mg of zinc sulfate (25 mg of zinc) can be taken with a soft drink such a ginger ale or Coca Cola, which, in our experience, reduces the incidence of gastrointestinal symptoms.

When taken on an empty stomach, zinc salts can produce gastrointestinal side effects

Therapeutic doses of 660 mg of zinc sulfate have been taken for more than a year by patients with sickle-cell disease. In some patients, evidence of copper deficiency anemia was detected, presumably due to the biological competition of zinc and copper (14,15). Megadoses of zinc (5 g/day) have been associated with the rapid development of copper deficiency. Copper nutrition, therefore, should also be monitored in patients on prolonged zinc therapy, and the recommendation to limit the daily dose of oral zinc to 40 mg/day (14) seems reasonable.

Parenteral Zinc Administration

Parenteral nutrition with alimentation solutions unsupplemented with zinc can result in progressive zinc defi-

ciency. A World Health Organization committee has calculated that 2.2 mg of zinc should be *absorbed* daily by the healthy adult. This is presumably the parenteral requirement for zinc in a normal individual. Shils earlier recommended empirically a trace mineral mixture containing 2 mg of zinc as zinc sulfate to be administered twice weekly (16). Recently an expert committee sponsored by the AMA established guidelines for the parenteral use of trace elements. They suggest a daily intake in the stable adult receiving TPA of 2.5–4.0 mg of zinc. It has been recommended that adult patients in an acute catabolic state receive an additional 2 mg. Individuals with superimposed intestinal fluid losses should be given 12.2 mg of zinc for each liter of small-intestinal fluid lost, or 17.1 mg for each kg of stool or ileostomy output (17).

These guidelines are only approximate as administration of parenteral zinc to supplement total parenteral alimentation is confounded by many factors. The intrinsic content of zinc in commercial preparations is highly variable, patients undergoing TPA may have increased requirements, excessive losses, or pre-existing zinc depletion due to the underlying illness, and zinc requirements may fluctuate over the course of parenteral nutrition. An important adjunct to parenteral alimentation is the serial evaluation of zinc status and appropriate adjustment of parenteral zinc dosage. Finally, the FDA has not yet approved intravenous administration of trace minerals, and therefore the zinc must be added separately to the infusion.

SUMMARY AND CONCLUSIONS

Zinc metabolism and nutrition are important considerations in the management of certain digestive diseases. One should be alert for the possible coexistence of zinc deficiency, perform the pertinent clinical observations, and request confirmatory laboratory tests, especially in conditions known to predispose to zinc deficiency. Unfortunately, the unequivocal determination of the zinc status of an individual with commonly available laboratory assays is not possible. Caution should be used in obtaining and interpreting plasma and serum zinc data, because exogenous contamination, on the one hand, and serum binding or internal redistribution factors, on the other hand, can obscure the nutritional meaning of a circulating zinc level. Collateral data should be obtained wherever possible.

Secondary zinc deficiency can occur in alcoholic cirrhosis, viral hepatitis, treated Wilson's disease, pancreatic insufficiency and cystic fibrosis, jejunoileal bypass procedures, malabsorption syndromes, and inflammatory bowel diseases. Acrodermatitis enteropathica is a specific malabsorption syndrome of zinc. The practitioner should also be aware of a possible etiological role for zinc in the epidemiology of esophageal cancer and of a potential therapeutic role for zinc sulfate therapy in benign gastric ulcer.

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The high-fiber, low-red-meat diet recommended by some for the prevention and treatment of certain colonic or bile acid disorders has a potential for producing zinc deficiency due to interference with the absorption of dietary zinc. Breast milk has advantages over cow's milk with respect to zinc bioavailability. Total parenteral alimentation is a situation in which definite attention to zinc nutrition is mandatory for the appropriate management of the patient, and one should be alert to the possibility that zinc supplementation of the intravenous infusion will be required. The administration of oral zinc therapy is indicated in certain well-defined situations. Gastrointestinal side effects are possible, but reducing the dose and giving it with a soft drink is preferable to administering oral zinc with meals.

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